## **CLAIMS**

1.) A pharmaceutical preparation which comprises in combination a bisphosphonate of formula I, or a physiologically acceptable and -cleavable ester or a salt thereof

wherein

X is hydrogen, hydroxyl, amino, alkanoyl, or an amino group substituted by  $C_1$ - $C_4$  alkyl, or alkanoyl;

R is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl and

Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles), or a pharmaceutically acceptable salt thereof or any hydrate thereof; and

a) a cat K inhibitor of formula V, or a physiologically acceptable and -cleavable ester or a salt thereof

$$R^{\frac{1}{2}} = L - \frac{1}{2} \times \frac{1}{2} \times \frac{R^3}{R^2} \times \frac{R^4}{R^5} = N$$
 (V)

wherein R<sup>1</sup> is optionally substituted (aryl, aryl-lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl or heterocyclyl-lower alkyl);

R<sup>2</sup> and R<sup>3</sup> together represent lower alkylene, optionally interrupted by O, S or NR<sup>6</sup>, so as to form a ring with the carbon atom to which they are attached, and R<sup>6</sup> is hydrogen, lower alkyl or aryl-lower alkyl;

R<sup>4</sup> and R<sup>5</sup> are independently H, or optionally substituted (lower alkyl or aryl-lower alkyl), - C(O)OR<sup>7</sup>, or -C(O)NR<sup>7</sup>R<sup>8</sup>, wherein R<sup>7</sup> is optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl, bicycloalkyl or heterocyclyl), and R<sup>8</sup> is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl, bicycloalkyl or heterocyclyl); or

R<sup>4</sup> and R<sup>5</sup> together represent lower alkylene, optionally interrupted by O, S or NR<sup>6</sup>, so as to form a ring with the carbon atom to which they are attached, and R<sup>6</sup> is hydrogen, lower alkyl or aryl-lower alkyl; or

 $R^4$  is H or optionally substituted lower alkyl and  $R^5$  is a substituent of formula  $-X^2-(Y^1)_n-(Ar)_{p^2}$  Q-Z wherein

Y1 is O, S, SO, SO2, N(R6)SO2, N-R6, SO2NR6, CONR6 or NR6CO;

N is zero or one;

P is zero or one;

 $X^2$  is lower alkylene: or when n is zero,  $X^2$  is also  $C_2$ - $C_7$ -alkylene interrupted by O, S, SO, SO<sub>2</sub>, NR<sup>6</sup>, SO<sub>2</sub>NR<sup>6</sup>, CONR<sup>6</sup> or NR<sup>6</sup>CO, and R<sup>6</sup> is hydrogen, lower alkyl or aryl-lower alkyl; Ar is arylene;

Z is hydroxyl, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sufonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y¹-lower alkylene or C2-C7-alkylene interrupted by Y¹;

 $X^1$  is -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, or  $-P(O)(OR^6)$ -, and  $R^6$  is as defined above;

Y is oxygen or sulphur;

L is optionally substituted –Het-, -Het-CH<sub>2</sub>- or –CH<sub>2</sub>-Het-, and Het is a hetero atom selected from O, N or S; and

X is zero or one; and

aryl in the above definitions represents carbocyclic or heterocyclic aryl; or alternatively

b) another class of cat K inhibitors of formula VII, or a physiologically acceptable and -cleavable ester or a salt thereof

$$R^{11} \longrightarrow R^{10} \qquad \qquad \text{VII}$$

$$HN \longrightarrow N \qquad C_{\geqslant N}$$

wherein

 $R^{10}$  is H,  $-R^{14}$ ,  $-OR^{14}$  or  $NR^{13}R^{14}$ ,

wherein  $R^{13}$  is H, lower alkyl or  $C_3$  to  $C_{10}$  cycloalkyl, and

R<sup>14</sup> is lower alkyl or C<sub>3</sub> to C<sub>10</sub> cycloalkyl, and

wherein R<sup>13</sup> and R<sup>14</sup> are independently, optionally substituted by halo, hydroxy, lower alkoxy, CN, NO<sub>2</sub>, or optionally mono- or di-lower alkyl substituted amino;

 $R^{11}$  is -CO-N  $R^{15}$   $R^{16}$ , -NH-CO-  $R^{15}$ , -CH<sub>2</sub>-NH-C(O)- $R^{15}$ , -CO-  $R^{15}$ , -S(O)-  $R^{15}$ , -S(O)<sub>2</sub>-  $R^{15}$ , -CH<sub>2</sub>-CO-  $R^{15}$  or -CH<sub>2</sub>-N  $R^{15}$   $R^{16}$ ,

wherein

 $R^{15}$  is aryl, aryl-lower alkyl,  $C_3$ - $C_{10}$ cycloalkyl,  $C_3$ - $C_{10}$ cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl,

 $R^{16}$  is H, aryl-lower alkyl, aryl-lower-alkenyl,  $C_3$ - $C_{10}$ cycloalkyl,  $C_3$ - $C_{10}$ cycloalkyl-lower alkyl, heterocyclyl-lower alkyl, or

wherein  $R^{15}$  and  $R^{16}$  together with the nitrogen atom to which they attached are joined to form an N-heterocyclyl group,

wherein N-heterocyclyl denotes a saturated, partially unsaturated or aromatic nitrogen containing heterocyclic moiety attached via a nitrogen atom thereof having from 3 to 8 ring atoms optionally containing a further 1, 2 or 3 heteroatoms selected from N, NR<sup>17</sup>, O, S, S(O) or S(O)<sub>2</sub> wherein R<sup>17</sup> is H or optionally substituted (lower alkyl, carboxy, acyl (including both lower alkyl acyl, e.g. formyl, acetyl or propionyl, or aryl acyl, e.g. benzoyl), amido, aryl, S(O) or S(O)<sub>2</sub>), and wherein the N-heterocyclyl is optionally fused in a bicyclic structure, e.g. with a benzene or pyridine ring, and wherein the N-heterocyclyl is optionally linked in a spiro structure with a 3 to 8 membered cycloalkyl or heterocyclic ring wherein the heterocyclic ring has from 3 to 10 ring members and contains from 1 to 3 heteroatoms selected from N, NR<sup>16</sup>, O, S, S(O) or S(O)<sub>2</sub> wherein R<sup>16</sup> is as defined above), and

wherein heterocyclyl denotes a ring having from 3 to 10 ring members and containing from 1 to 3 heteroatoms selected from N, NR<sup>17</sup>, O, S, S(O) or S(O)<sub>2</sub> wherein R<sup>17</sup> is as defined above), and

wherein R<sup>15</sup> and R<sup>16</sup> are independently, optionally substituted by one or more groups, e.g. 1-3 groups, selected from halo, hydroxy, oxo, lower alkoxy, CN or NO<sub>2</sub>, or optionally substituted (optionally mono- or di-lower alkyl substituted amino, lower-alkoxy, aryl, aryl-lower alkyl, N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein the optional substitution comprises from 1 to 3 substituents selected from halo, hydroxy, lower alkoxy, lower alkoxy-lower alkyl, lower alkoxy-carbonyl, CN, NO<sub>2</sub>, N-heterocyclyl or N-heterocyclyl-lower alkyl, or optionally mono- or di-lower alkyl substituted amino;

 $R^{12}$  is is independently H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl,  $C_3$ - $C_{10}$ cycloalkyl,  $C_3$ - $C_{10}$ cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl), and wherein R2 is optionally substituted by halo, hydroxy, oxo, lower alkoxy, CN,  $NO_2$ , or optionally mono- or di-lower alkyl substituted amino.

for simultaneous, sequential or separate use.

- 2.) The pharmaceutical preparation according to claim 1; whereas its use is for the treatment of malignant diseases, bone metastasis, cancer cell growth, or/and cancer therapy-induced bone loss.
- 3.) The use of a cathepsin K inhibitor according to claim 1 for the preparation of a medicament, for use in combination with a bisphosphonate according to claim 1 for treatment of a malignant disease, bone metastasis, cancer cell growth or/and cancer therapy-induced bone loss; or a method of treating a patient suffering from a malignant disease, bone metastasis, cancer cell growth, or/and cancer-therapy-induced bone loss comprising administering to the patient an effective amount of a bisphosphonate according to claim 1 and an effective amount of a cathepsin K inhibitor according to claim 1.
- 4.) The use of a cathepsin K inhibitor according to claim 1 for the preparation of a medicament, for use in combination with a bisphosphonate according to claim 1 for treatment of a benign disease, bone loss disease, osteoporosis, osteoarthritis; or

a method of treating a patient suffering from a benign disease, bone loss disease, osteoporosis, osteoarthritis comprising administering to the patient an effective amount of a bisphosphonate according to claim 1 and an effective amount of a cathepsin K inhibitor according to claim 1.

- 5.) A pharmaceutical composition comprising Zoledronic Acid and a cathepsin K inhibitor for the inhibition of bone metastasis, cancer cell growth or/and inhibition of cancer-therapy-induced bone loss.
- 6.) A pharmaceutical preparation according to claim 1 or 2, a use or a method according to claims 3 or 4 or a pharmaceutical composition of claim 5, in which the cathepsin K inhibitor is selected from the group of N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-methyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-ethyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-isopropyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-benzyl-piperazin-1-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-propyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]- 4-[1-(2-methoxy-ethyl)-piperidin-4-yl]-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-isopropyl-piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-cyclopentyl -piperidin-4-yl)-benzamide; N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(1-methyl-piperidin-4-yl)-benzamide, and N-[1-(Cyanomethyl-carbamoyl)-cyclohexyl]-4-(piperidin-4-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethylpropylamino)-pyrimidin-5-ylmethyl]-4-(1-propyl-piperidin-4-yl)-benzamide, N-[2-Cyano-4-(2,2dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-methyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-[1-(2-methoxy-ethyl)-piperidin-4yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-propylpiperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-2,2dimethyl-3-[4-(4-methyl-piperazin-1-yl)-phenyl]-propionamide, N-[2-Cyano-4-(2,2-dimethylpropylamino)-pyrimidin-5-ylmethyl]-2,2-dimethyl-3-[3-(4-methyl-piperazin-1-yl)-phenyl]propionamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4-ethylpiperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-(4isopropyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-

ylmethyl]-4-[4-(2-ethoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethylpropylamino)-pyrimidin-5-ylmethyl]-4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-piperazin-1-yl-benzamide, 4-(4-{[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-carbamoyl}-phenyl)-piperazine-1carboxylic acid tert-butyl ester, 4-(3-{[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5ylmethyl]-carbamoyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester, N-[2-Cyano-4-(2,2dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-methyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-ethyl-piperazin-1-yl)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(4-isopropyl-piperazin-1-yl)benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(2-methoxyethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5ylmethyl]-3-[4-(2-ethoxy-ethyl)-piperazin-1-yl]-benzamide, N-[2-Cyano-4-(2,2-dimethylpropylamino)-pyrimidin-5-ylmethyl]-4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-(2-dimethylamino-ethoxy)-4methoxy-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4dimethylaminomethyl-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5ylmethyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide, N-[2-Cyano-4-(2,2-dimethylpropylamino)-pyrimidin-5-ylmethyl]-4-[1-(2-methoxy-ethyl)-piperidin-4-ylmethyl]-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-4-methoxy-3-(2-piperidin-1-ylethoxy)-benzamide, N-[2-Cyano-4-(2,2-dimethyl-propylamino)-pyrimidin-5-ylmethyl]-3-[4-(4ethyl-piperazin-1-yl)-phenyl]-2,2-dimethyl-propionamide or pharmaceutically acceptable salt thereof.

7.) A pharmaceutical preparation according to claim 1 or 2, a use or a method according to claims 3 or 4 or a pharmaceutical composition according to claim 5, in which the cat K inhibitor is N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-(4-(1-propyl)-piperazin-1-yl)-benzamide or a pharmaceutically acceptable salt thereof and the bisphosphonate is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or pharmacologically acceptable salts thereof.